REMARKS

Applicants have amended the claims throughout to recite administration of the enumerated dosages of PEG_{12000} interferon alpha. Support for these amendments can be found in the specification, for example, in the paragraph bridging pages 4-5. A minor typographical error in claim 15 has also been corrected by amendment. No new matter has been added by virtue of the foregoing amendments to the claims.

The present invention provides, for the first time, a therapy for melanoma which is both more efficacious and more tolerable than previously available interferon therapies.

In the prior responses of record, Applicants have clearly established that unpegylated interferon alpha and pegylated interferon alpha are structurally and functionally distinct drugs with different pharmacokinetic properties. These differences are critical because a particular pharmacokinetic property, such as a patient's total exposure to a drug (AUC) or the peak plasma level of the drug (C_{max}), is often essential for successfully treating a specific disease. Applicants have also shown that knowledge of the pharmacokinetic properties of unconjugated interferon alpha in the same or different diseases would not be predictive of the pharmacokinetic properties that PEG_{12000} interferon alpha would possess at the doses required to treat melanoma. Applicants determined, for the first time, that administration of PEG_{12000} interferon alpha to a patient provides lower peak plasma levels yet prolonged total drug exposure of interferon alpha activity as compared to administration of unconjugated interferon alpha. Applicants further determined that these parameters provided

optimal anti-melanoma activity when PEG_{12000} was administered to patients according to the specific dosage regimens set forth in the pending claims. By so doing, Applicants provided a treatment method that had been previously lacking in the field – a therapy for the treatment of melanoma which is both more efficacious and more tolerable than previously available interferon therapies.

In this Amendment and Response, Applicants have limited the claims to the administration of PEG_{12000} interferon alpha within the cited dosage ranges to treat melanoma. The accompanying Declaration under 37 C.F.R. § 1.132 of Dr. David Cutler (hereafter "the Cutler declaration") provides normalized data that substantiates the fact that the above parameters are achieved when PEG_{12000} interferon alpha is administered to humans according to the methods of the amended claims.

The Rejections under 35 U.S.C. §103

The Examiner has maintained the rejection of claims 1, 3-7, 9, 11, 12, 14-17 and 21-40 as allegedly being unpatentable over Kirkwood *et al.*, J. Clin. Oncol. 14(1): 7-17, 1996 (hereafter "Kirkwood") in view of Gilbert *et al.*, United States Patent 5,951,974 (hereafter "Gilbert"), in view of Glue *et al.*, United States Patent 5,908,621 (hereafter "Glue"), and further in view of Talpaz *et al.*, Blood 92(10): 251a, 1998 (hereafter "Talpaz").

The Examiner has also maintained the rejection of claims 1, 3-7, 10, 11, 13 and 14 as allegedly being unpatentable over Creagan *et al.*, J. Clin. Oncol.

13(11): 2776-2783, 1995 (hereafter "Creagan") in view of Gilbert, and further in view of Glue for the reasons of record.

In response to Applicants' arguments that arrival at an optimum dose range for pegylated interferon is an unexpected result and that the administration of pegylated interferon alpha at the dose required to treat melanoma results in lower peak plasma levels of interferon yet prolongs total drug exposure as compared to administration of unconjugated interferon alpha, the Examiner asserts that "this argument appears to be relevant to some forms of pegylated interferon and not for others, and the claims are not limited to those forms for which this argument applies." The Examiner cites Gilbert, col. 13-col. 14 and Table 5 in support of this assertion.

In the present Amendment and Response, Applicants have:

a) limited the claims to recite administration of PEG_{12000} interferon alpha, and

b) submitted a Declaration under 37 C.F.R. § 1.132 of Dr. David Cutler (hereafter "the Cutler Declaration").

The Cutler Declaration provides normalized data that substantiates Applicants' previous assertions that the optimal pharmacokinetic parameters described above are achieved when PEG_{12000} interferon alpha is administered to humans according to the claimed methods. Specifically, the Cutler Declaration establishes that when either 2 micrograms/kg/wk of PEG_{12000} interferon alpha or 3 MIU of Intron A were administered to humans to treat melanoma, the total drug exposure (AUC) was significantly higher than that when unpegylated interferon alpha was administered according to the same protocol (Cutler

Declaration ¶ 7). Likewise, administration of the same dosages of PEG_{12000} interferon alpha and Intron A resulted in a lower peak plasma level (Cmax) than that for unpegylated interferon alpha administered according to the same protocol (Cutler Declaration ¶ 6). These data were then normalized to clinical doses of 3 μg/kg for PEG and 25 MIU for Intron A. Therefore, the amended claims are commensurate in scope with Applicants' showing of unexpected results.

The Gilbert data cited by the Examiner is irrelevant to the patentability of the amended claims because the methods used to generate this data do not fall within the limitations of the amended claims. Firstly, Applicants' broadest claim requires administration of PEG_{12000} interferon alpha to "a patient having melanoma which has been surgically removed" (claim 1). In Gilbert, interferon alpha has been administered to rats. Secondly, the doses administered to the rats in Gilbert do not fall within the dosage ranges of claim 1.

In view of the foregoing amendments and the Delcaration submitted concurrently herewith, applicants submit that the obviousness rejections should be withdrawn.

CONCLUSION

Applicants request that the Examiner consider the foregoing amendments and remarks, allow the pending claims and pass this application to issue.

If the Examiner should have any questions regarding this response or application, she is encouraged to contact the undersigned.

Respectfully submitted,

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